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## R-Bendamustine in the treatment of nodular lymphocyte-predominant Hodgkin lymphoma

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### Introduction

Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) is an indolent Hodgkin lymphoma (HL) entity counting for ~5% of all HLs [1]. However, it seems to be a biologically distinct disease with a favorable prognosis with an 80% 10-year overall survival without any lymphoma treatment [2]. Unlike in classical Hodgkin lymphoma (cHL), neoplastic cells are positive for CD20. Due to the indolent nature of the disease, deaths caused by NLPHL without further histological progression are uncommon [3]. The clinical course of the disease is indolent, but multiple relapses occur occasionally [4]. Unlike in cHL, a transformation to other lymphomas such as T-cell rich B-cell lymphoma or diffuse large B-cell lymphoma may occur [4,5].

Most patients are treated with a regimen developed for cHL. Treatment with cHL protocols leads to complete response (CR) in >95% of cases [6]. However, it has been suggested that NLPHL would not require as aggressive treatment as cHL. Therefore, chemotherapy followed by radiation therapy (RT) may not be the best option for NLPHL [7]. The majority of NLPHL patients die of cardiac disease or secondary malignancy, which are often consequences of previous lymphoma treatments [3]. For these reasons, there is an unmet clinical need to find an effective treatment regimen with less long-term toxicity.

The CD20 antibody rituximab is often used in advanced-stage, recurrent and refractory NLPHL [8]. Rituximab has been shown to induce good response rates (RRs) in first-line treatment and in relapsed and refractory cases [9,10].

In the last 5 years in Oulu University Hospital, NLPHL patients have been treated with R-bendamustine to minimize therapy-associated toxicity. In the present work, we retrospectively collected and analyzed the data to evaluate the feasibility of this strategy.

### Material and methods

This is a retrospective registry study. We collected clinical data from hospital records of NLPHL patients who were treated with R-Bendamustine either in first line or after the first relapse. Data was collected from Oulu University Hospital in Finland.

Patients were diagnosed between 2001 and 2016. The diagnoses were reviewed by experienced hematopathologists. Information such as age, stage, ECOG performance status, details of treatment, possible relapses and the current status were investigated. Event free survival (EFS) was calculated from the date of first day of first chemotherapy cycle up to the date of the disease relapse or the last follow-up date. Patients lost from follow-up were censored at the last day of documented survival.

### Results

In total, nine patients treated with R-bendamustine were found. Patient demographics are given in Table 1. The median age was 46.5 years. Of patients 7/9 were male, 8/9 of patients presented advanced-stage disease and 1/9 of patients had B-symptoms. The median follow-up time after NHL treatment was 34.0 months (14–79).

### Treatments

Seven patients were treated frontline and two in the first relapse. From relapsed patients, one patient was treated with RT only in frontline and one was treated with AVBD in frontline.

### Treatment outcomes

RR in the whole patient group was found to be 9/9 and CR was achieved in 9/9 of the patients. After a median follow-up

**Table 1.** Patient demographics.

Characteristic	Result	Data available (n)
Age (years)	Median 46.5 (19–61)	9
Sex		9
Male	7/9	
Women	2/9	
Stage		9
1	1/9	
3	6/9	
4	2/9	
B-symptoms	1/9	9
LDH		6
Elevated	1/6	
ECOG performance status		5
0	5/5	
Line of treatment		9
First line	7/9	
First relapse	2/9	
Previous treatments		
ABVD	1	
RDT	1	

period of 34 months, the EFS was 9/9. During our follow-up, none of the patients have relapsed.

### Toxicity

One patient had been changed to R-CEOP therapy after two cycles of R-bendamustine due to an allergic reaction related to bendamustine.

### Discussion

In the present work, we report that with relatively short follow-up time that the treatment outcome of R-bendamustine is excellent in NLPHL patients.

NLPHL is an indolent disease with an insignificant risk of death without a histological transformation. There is a series of 23 patients with NLPHL published with median survival of 16 years without any lymphoma treatment [11].

NLPHL has traditionally been treated like other HL subtypes. Treating NLPHL with cHL regimens provides good results in the term of disease control. In advanced-stage patients treated with ABVD, 5- and 10-year OS of 89 and 83.5% have been reported [12]. With a small number of patients treated with R-ABVD, the estimated 6-year PFS and OS of 75 and 100% have been shown [13]. One of the major concerns for the therapy for HL is long-term toxicity [14]. Actually, the treatment-induced side effects cause higher mortality than the disease itself [15].

The most common nonmalignant causes of death in patients treated for HL are the cardiovascular diseases. RT and chemotherapy are both linked to an increased risk of cardiac mortality. Patients treated with ABVD have a 7.8 times higher risk of death from myocardial infarction than the general population and patients who received mediastinal RT have 2.6 times higher risk of myocardial infarction than patients treated without RT [16]. Combined use of chemotherapy and RT increase the risk of cardiac toxicity more than either of the treatment methods alone [17].

Another group of important late effects of HL treatment are secondary malignancies. Both RT and chemotherapy are associated with higher risk of secondary malignancies,

increasing the risk of leukemia, breast cancer, lung cancer and gastrointestinal cancer [18]. In NLPHL, secondary malignancies have been found to be the main cause of death during a long follow-up on patients treated with RT only [3].

There is not much experience of the use of NHL treatments in NLPHL patients. Fanale et al. [11] have treated 59 advanced-stage patients with R-CHOP showing 5- and 10-year PFS of 88.5 and 59.3%. The 5-year cumulative incidence of transformation was shown to be 2%. Another report of 12 patients with advanced-stage disease treated with R-CHOP has been published with an overall RR of 100% and CR rate of 90%. No relapses or transformations were detected within the median follow-up time of 42 months [19]. In contrast to classical Hodgkin's lymphoma, NLPHL is a CD20 positive disease [1,6], which enables the use of CD20 antibody rituximab. The use of rituximab only and rituximab maintenance without chemotherapy seems to be effective but provides only short remissions [20].

Bendamustine is a drug that offers a favorable risk-benefit profile. One important issue is that with bendamustine it's possible to avoid anthracycline therapy and the potential risk of anthracycline cardiomyopathy. With NHL patients, R-bendamustine has been used for patients with indolent disease and in aggressive disease in patients not eligible for R-CHOP due to cardiac insufficiency [21]. The most common side effects of bendamustine are myelosuppression and infections [22]. Myelodysplastic syndromes have been connected to the use of bendamustine [23] but the incidence of is not well-known [24].

There are so far no data available of NLPHL patients treated with R-bendamustine. In this retrospective analysis, we observed a 100% CR rate and a 100% PFS rate with a median follow-up of 34 months. The data presented here indicates that R-bendamustine might serve as a well-tolerated and effective option for the treatment of NLPHL.

Approximately 20% of NLPHL patients have advanced-stage disease [3]. Advanced-stage NLPHL is a more aggressive disease with poorer RRs and OS. In a series of 55 patients, patients with limited-stage disease (I–II) had 5-year PFS of 76.4% while those with advanced-stage disease (III–IV) show a 5-year PFS of only 29.9% [25]. According to Swedish registry data, patients with early-stage disease (I–IIA) had a 10-year OS of 85% and with advanced-stage disease (IIB–IV) the 10-year OS was 64% [26]. In the present patient group, 8/9 of cases had advanced-stage disease. Despite the fact that most patients treated with R-bendamustine had an advanced-stage disease, good treatment responses were achieved.

Due to the rarity of this disease only a limited number of patients were eligible for this study. The patient group is also heterogeneous, and the follow-up time for the patients was quite short. These results should, thus, be interpreted with caution.

### Conclusions

This is a preliminary study showing that R-bendamustine is promising candidate for the therapy of NLPHL. However, the

results of this study should be verified in larger prospective trials.

## Disclosure statement

No potential conflict of interest was reported by the authors.

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## LETTER TO THE EDITOR

## Adaptive radiotherapy in head and neck cancer is required to avoid tumor underdose

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